PATENT SPECIFICATION 993,138

NO DRAWINGS.

993,138

Date of Application and filing Complete Specification:
Jan. 31, 1962. *No. 3623/62.*

Application made in United States of America (No. 154,348) on Nov. 22, 1961.

Complete Specification Published: May 26, 1965.

Index at Acceptance:—A5 B(3, 4).

Int. Cl.:—A 61 k 3/10.

COMPLETE SPECIFICATION.

Improvements in the Preparation of Vitamin-Containing Beadlets.

We, CHAS. PFIZER & CO. INC., a corporation organized under the laws of the State of Delaware, United States of America, of 11 Bartlett Street, Brooklyn, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to vitamin-containing products, more particularly to a vitamin preparation composed of gelled, colloidal particles which are insoluble in water and gastric fluid but soluble in intestinal fluid, and having dispersed and imprisoned therein, a high proportion of a vitamin as hereinafter defined.

Throughout this specification the word "vitamin" except where the context requires that it should bear its usual meaning, means at least one oil-soluble vitamin, at least one ester or salt of an oil-soluble vitamin, or mixtures thereof. For example, it encompasses vitamin A palmitate, vitamin A acetate and vitamin K sodium bisulphite.

According to the present invention there is provided a process for preparing a vitamin preparation, which process comprises forming a particle comprising a vitamin as hereinbefore defined, gelatin or other gellable, denaturable polypeptide colloid and an edible plasticizer for the said gelatin or other gellable, denaturable polypeptide colloid, the ratio of the weight of the said vitamin to the total weight of the materials constituting the particle being from 0.1 to 1 to 0.55 to 1, and rendering at least the surface layers of the particle insoluble in water and gastric fluid U.S.P. but soluble in intestinal fluid U.S.P. by contacting the exterior or the interior of the particle with a denaturing agent for the said colloid and, if necessary, heating the particle, or, alternatively, rendering at least the surface layer of the particle insoluble in water and gastric fluid U.S.P. but soluble in intestinal fluid U.S.P. by heat treatment only.

In carrying out this invention the vitamin as hereinbefore defined is thoroughly dispersed in an aqueous solution containing gelatin or other gellable, denaturable polypeptide colloid and an edible plasticizer which is a sugar-like material i.e. one containing glucose or invert sugar, such as corn syrup, molasses or honey. This aqueous despersion may then be suspended in an edible oil, whether vegetable or mineral, or in a mixture of an oil and a water-miscible solvent e.g. propylene glycol or ethylene glycol, in the form of small droplets of the desired particle size. The dispersion is preferably warmed before the droplets set to form beadlets, and, after the desired size of droplets have been obtained, the oil suspension is chilled, in order to gel the beadlets quickly. If the vitamin as hereinbefore defined is solid, the aqueous dispersion may be heated above the melting point thereof, in which case an emulsion of the molten vitamin in the aqueous gelatin or other polypeptide colloid solution is obtained. On cooling, the suspension of droplets of such emulsion in the oil, in order to gel the beadlets, the vitamin, as hereinbefore defined again crystallizes and is imprisoned in finely divided, solid form within the beadlets, thus effectively preventing the high proportion of vitamin that is utilized from escaping to the surface of the beadlets. After the beadlets are filtered and dried, the beadlets may be suspended in a liquid containing the denaturating agent, e.g. formaldehyde. After this treatment, the beadlets are again separated by decantation and dried. Alterna-

tively, the denaturant may be introduced at various stages of the beadlet production. More particularly, by way of example, the denaturant may be introduced when the emulsion is added to the edible mineral or edible vegetable oil or when the aforementioned mixture is chilled. The advantage of the latter methods is that when the denaturating agent is introduced during the production of the beadlet, the beadlet will be thoroughly impregnated by the denaturant. Therefore, a more consistent and uniform product is obtained.

The glucose, honey or other such material serves as a plasticizer, that is they make the gelatin or other polypeptide colloid matrix more flexible and prevent cracking and shattering. They also help to prevent access of the air to the vitamin contained within the beadlets, because the plasticized, gelled colloid has a more closely knit, less porous structure. Furthermore, these plasticizers make the product more palatable.

During the preparation of the beadlets and, in particular, while the materials are at an elevated temperature, the stability of the product may be improved by removing the materials from contact with air. This may most easily be done by using a blanket of inert gas, such as carbon dioxide or nitrogen, over the surface of the aqueous dispersion, particularly when the latter is being stirred. For the same purpose, it has been found advisable to use boiled, air-free water in preparing the aqueous solution of gelatin or other polypeptide colloid and plasticizer in which the vitamin is dispersed. Once the droplets in oil have been gelled and at least partially dried, there is no longer any advantage in using the blanket of inert gas.

To enhance the stability of vitamins as hereinbefore defined which are prone to oxidation, antioxidants and synergistic mixtures thereof may be employed. The antioxidants and mixtures thereof which may be employed have been described in U.S. Patent 2,935,449.

After the beadlets or granules with or without the denaturant have been gelled by cooling, they may be removed from the suspending edible mineral or vegetable oil by filtration or by other suitable means. The residual oil may be washed from the surface of the granules with a suitable solvent. The small beadlets may then be dried in an atmosphere of suitably low humidity. The beadlets obtained by this procedure are inherently dry and oil-free. If the denaturant employed is either formaldehyde or glyoxal and it is admixed with the other starting materials during the production of the beadlets, the beadlets obtained will be insoluble in water and gastric fluid. However, if the beadlets are prepared without the addition of formaldehyde or glyoxal the resulting beadlets are soluble in water and gastric fluid. Upon addition of these beadlets to *n*-hexane and admixing this suspension with a solution of formaldehyde or glyoxal, the beadlets when separated and dried will no longer exhibit the aforementioned solubility. If denaturing agents, other than formaldehyde or glyoxal are employed for example, dihydroxyacetone, the beadlets must be heated to temperatures from 75° C. to 100° C. for a period of 0.5 to 4 hours, in order to obtain beadlets that are insoluble in water and gastric fluid but soluble in intestinal fluid. This heating is normally conducted after the treated beadlets have been formed and may be during the drying of the beadlets. Whether the denaturant, other than formaldehyde or glyoxal, is added during the formation of the beadlets or whether the formed beadlets are subsequently treated, the treated, formed beadlets must be subjected to elevated temperatures in order to form a beadlet product which is insoluble in water or gastric fluid but soluble in intestinal fluid.

It has been found that certain ranges or proportions of the various ingredients used in the preparation of these compositions are most suitable. The proportion of denaturant employed to the dry beadlet weight may be 1% to 10% in the cases where the polypeptide colloid is gelatin and the denaturing agent is formaldehyde or glyoxal. The amount of agent employed will normally vary with the degree of denaturation desired and can easily be determined by those skilled in the art. In the case of gelatin and dihydroxyacetone, 1% to 30% is suitable. The quantity of antioxidant or synergistic mixtures thereof which is employed is dependent upon the particular vitamin and antioxidant or synergistic mixture employed. The proportion of weight of corn syrup, or other suitable gelatin plasticizer of similar water content, to gelatin is preferably from 0.4: 1 to 1.5: 1. The value of 0.8: 1 seems to be approximately the optimum for this plasticizer. The proportion by weight of water to gelatin may be from 1.5: 1 to 2.5: 1, and the lower part of this range seems to be particularly suitable, e.g. 1.5: 1 to 1.9: 1. The ratio of the weight of the vitamin as hereinbefore defined to the total weight of the materials constituting the particle (e.g. gelatin+corn syrup+vitamin) ranges from 0.1: 1 to 0.55: 1. Of course, lower proportions may be used, however, employing such proportions would not have any economic advantage. The vitamins which are normally employed are vitamin A, D, E and K and/or their pharmaceutically acceptable esters.

It is to be understood that various materials specifically mentioned above may

be replaced by comparable materials with similar properties e.g. the corn syrup may be replaced by honey or by molasses or by invert sugar syrups of various kinds. The edible oil which is used as a suspending medium in the formation of the vitamin-containing beadlets may also be varied considerably. It may be edible mineral oil, corn oil, soybean oil, cotton oil, sesame oil or any other such material. The oil should have a viscosity of at least 100 Saybolt units at room temperature or the beadlets will not form properly when the aqueous gelatin dispersion is stirred into it. The denaturant employed may be foramldehyde or glyoxal and when either of these agents are employed heating of the treated beadlets is not necessary to produce a product which is insoluble in water or gastric fluid U.S.P. but soluble in intestinal fluid U.S.P. Other agents which require heating to produce the aforementioned beadlet properties are dihydroxyacetone, calcium oxide, egg albumin and acetaldehyde. The beadlets may also be denatured without the addition of a denaturant by simply heating the untreated, formed beadlets. Although this is a simple procedure, the disadvantages are that higher temperatures from about 110° C. to about 120° C. are necessary to denature the beadlets; in many cases this hardening is reversible; and longer period of heating are required. Since many vitamins are thermolabile these higher heating temperatures and longer heating periods will also cause greater losses of vitamin potency.

The beadlets formed by the process of this invention may also contain ingredients in addition to vitamins as hereinbefore defined, for example, other medicinals which are prone to decomposition by oxidation or hydrolysis. Alternatively, these treated beadlets may be employed when the particular medicinal is absorbed from the intestine, thus delivering the active component intact to the site of absorption.

The advantage of the treated beadlets is readily demonstrated by the solubility exhibited by the active component in distilled water, gastric fluid U.S.P. and intestinal fluid U.S.P. For example, the release of vitamin A palmitate from untreated beadlets, beadlets treated with formaldehyde and beadlets treated with dihydroxyacetone was compared in the aforementioned solvents. In order to obviate any differences in results due to variance of particle size in each of the three heretofore mentioned type beadlets, each type was separated into various mesh sizes by using metal screens. Only similar mesh sizes were compared. Thereafter, eight 250 mg. ± 5 mg. samples of the untreated, of the formaldehyde treated and of the dihydroxyacetone treated beadlets of a specific mesh range were placed in 250 ml., glass stoppered, volumetric flasks. To each flask there was added either 15 ml. of distilled water, Gastric fluid U. S. P. or Intestinal fluid U. S. P., depneding on the particular test being conducted. Subsequently, 15 ml. of n-octanol were added to each flask and the samples attached to a "Wrist Action Shaker" whose shaking speed was controlled by a rheostat. The bottoms of the flasks were immersed in a constant temperature water bath at 37° C. ± 1° C. and the shaking initiated.

Samples were removed from the water bath at specific time intervals and after 2 minutes, when the octanol solution was completely separated, a 5 ml. aliquot was removed for analysis. The samples were assayed by diluting the 5 ml. octanol sample with isopropanol and determining its optical density at 327 mμ, using a Beckman DU Spectrophotometer. The amount of vitamin A palmitate released was calculated by the following formula:

$$\text{units of Vitamin A palmitate released} \; \epsilon \, {}^{1\%}_{1\,\text{cm.}} \text{ at } 327\ \text{m}\mu = \frac{3000 \cdot 1.817 \times 10^3}{975} \cdot \text{from sample}$$

wherein $\epsilon \, {}^{1\%}_{1\,\text{cm.}}$ 327 mμ is the extinction coefficient in a 1 cm. cell containing a 1% solution of the material at 327 mμ of 5 ml. of the octanol layer diluted to 100 ml. with isopropanol; 3000 is the dilution factor; 1.817×10^3 is the number of units of vitamin A per mg. of vitamin A palmitate; and 975 is the $\epsilon \, {}^{1\%}_{1\,\text{cm}}$ 327 mμ for vitamin A palmitate.

Tables, I II and III indicate the units of vitamin A released from the treated and untreated beadlets as a function of time in distilled water, Gastric fluid U. S. P. and Intestinal fluid U. S. P. The percent released per unit time, as expressed in the three tables, is based on a calculated content of 62,500 units of vitamin A in 0.250 g. of beadlets.

TABLE I

Vitamin O Palmitate Released from a 0.250 G. Sample of Beadlet (40—50 mesh) in Distilled Water

Beadlet Type

Time (Minutes)	Untreated Beadlet		Formaldehyde-Treated Beadlet		Dihydroxyacetone-Treated Beadlet	
	Units	Percent	Units	Percent	Units	Percent
30	3,600	5.8	0	0	0	0
60	21,100	33.8	0	0	0	0
120	46,800	74.8	0	0	0	0
180	59,900	95.6	0	0	0	0
330	60,500	97.0	0	0	0	0
360	—	—	800	1.2	0	0

TABLE II

Vitamin A Palmitate Released from a 0.20 G. Sample of Beadlet (40—50 mesh) in Gastric Fluid USP

Beadlet Type

Time (Minutes)	Untreated Beadlet		Formaldehyde-Treated Beadlet		Dihydroxyacetone-Treated Beadlet	
	Units	Percent	Units	Percent	Units	Percent
15	3,660	5.9	0	0	0	0
30	6,620	10.5	0	0	0	0
60	17,150	28.4	0	0	0	0
90	30,000	48.0	0	0	0	0
120	54,500	86.5	0	0	0	0
180	55,200	88.5	0	0	0	0
300	62,500	100.0	0	0	0	0
360	—	—	7,400	11.8	0	0

TABLE III

Vitamin A Palmitate Released from a 0.250 G. Sample of Beadlet (30—40 mesh) in Intestinal Fluid USP

Beadlet Type

Time (Minutes)	Untreated Beadlet		Formaldehyde-Treated Beadlet		Dihydroxyacetone-Treated Beadlet	
	Units	Percent	Units	Percent	Units	Percent
30	16,436	26.3	36,058	57.5	47,351	75.6
60	63,000	100.1	48,641	77.8	62,613	100.0
120	61,498	98.5	—	—	62,613	100.0
180	67,089	107.0	41,029	65.5	62,613	100.0
330	54,700	87.5	50,313	80.5	57,017	91.2

It is evident from the data presented in Tables I, II and III that denaturing agents, such as formaldehyde and dihydroxyacetone prevent the penetration of moisture into the beadlet under neutral and acidic conditions hence, delaying the release of vitamin A palmitate. In intestinal fluid, however, the combination of enzymes and pH are effective in disrupting the beadlet and liberating the vitamin. This is a desirable property, particularly for vitamin A, which was shown by Murthy *et al in Nature*, Volume 189, page 482 (1961) to be absorbed from the intestinal tract and to be prone to acidic hydrolysis. Analysis of the aforementioned data, also shows that after the treated beadlet has been exposed to gastric conditions for 6 hours, vitamin A palmitate begins to be released. This condition is of no consequence, since the normal emptying time for the stomach is 3 to 4.5 hours, as reported by Best and Taylor in their text *Physiological Basis of Medical Practice*, 6th Edition, page 566, (1955).

The following examples are given by way of illustration.

Example I

128 Grams of commercially available corn syrup were added to 240 mls. of water. The mixture was heated to 65° C. and 160 grams of a high-quality pharmaceutical-grade gelatin, were added. The mixture was stirred and heated at 75° C. until a solution was obtained. 102 Grams of vitamin A palmitate, 3 grams of 6 - ethoxy - 2,2,4 - trimethyl-1,2 - dihydroquinoline and 2 grams of butylated hydroxy anisole were then added to the solution and rapidly stirred to disperse the vitamin completely. The temperature at this point dropped to 65° C. To the resultant mixture were added 480 mls. of edible mineral oil which had been heated to 65° C. The mixture was agitated until a fine suspension of gelatin globules or droplets in the oil was obtained. The rate of stirring and the type of stirrer may be varied to obtain the desired particle size. When the desired particle size was obtained, agitation was continued and 6 ml. of a 37% formaldehyde solution were added to the suspension, while the suspension in oil was cooled by means of an ice bath to 10° C. To the chilled suspension were then added 800 mls. of isopronanol which had previously been cooled to 10° C. The mixture was stirred for 5 minutes and the gelled beadlets containing vitamin A palmitate were filtered on a Buchner funnel. The product was then added to a litre of isopropanol at 10° C. The mixture was stirred for 5 minutes and the product was again filtered. This served to remove most of the residual oil and also served partially to dehydrate the gelatin granules.

The product was then placed on trays in a low humidity (10—20%) atmosphere at room temperature for 15 to 16 hours. The dried product still retained a slight film of oil on the surface of the particles. The dried product was washed twice with 750 millilitre portions of acetone to complete the dehydration and it was then air dried. Since the particle size is not completely uniform, although a high percentage may be prepared within a fairly uniform particle size range, the product may be screened to remove particularly fine beadlets.

The product obtained as described above was very suitable for use in the preparation of pharmaceutical products such as tablets or capsules, either of vitamin A alone or in the form of multi-vitamin preparations. The fine beadlets were found to be easily incorporated in various enriched foods or in animal feeds allowing for uniform distribution throughout the mixture. The stability to aqueous and acidic degradation and mechanical strength of the product was excellent.

Example II

84 Grams of commercially available corn syrup were added to 306 grams of water. The mixture was heated to 65° C. and 204 grams of gelatin in the form of fine granules were added. The mixture was stirred at 75° C. until a solution was obtained. To this solution were added 102 grams of vitamin E acetate, 1 gram of sodium ascorbate and 1 gram of sodium citrate. After stirring until a uniform dispersion of the vitamin was obtained, 500 mls. of corn oil were added. The mixture was stirred rapidly at 65° C. until uniform globules of gelatin averaging about 1 mm. in diameter were obtained. The suspension was then cooled to about 5° C. and 800 mls. of precooled isopropanol were added. After having been stirred for a short time at low temperature, the chilled droplets were filtered, suspended in isopropanol at 10° C., stirred for a short time and refiltered. The product was dried in a low humidity atmosphere. This product was suspended in 300 ml. of hexane and 10 ml. of a 37% formaldehyde solution added to this slurry and the mixture stirred for approximately 5 minutes. Thereafter, the suspended beadlets were filtered and air dried and further dehydrated by means of two acetone washes. The resulting beadlets when tested were insoluble in gastric fluid U.S.P. and water but soluble in intestinal fluid U.S.P.

Example III

A suspension of gelatin beadlets in soybean oil was prepared as described in Example I. The following materials were used for the preparation of this gelable compositions:

	Grams
Gelatin	180
Honey	108
Vitamin K sodium bisulphite	102
Water	207

After stirring the suspension in oil containing 8 grams of glyoxal until a uniform product of the desired particle size had been obtained, the mixture was cooled to set the gelatin beadlets and recrystallize the vitamin K salt, and the product was isolated, washed and dried as described previously.

EXAMPLE IV

A composition was prepared containing 40 grams of gelatin, 32 grams of corn syrup, 40 grams of vitamin D_2, 0.36 grams of butylated hydroxy anisole, 0.64 grams of butylated hydroxy toluene and 100 ml. of water. This mixture was stirred and heated until a uniform dispersion of the vitamin in the aqueous medium was obtained. The dispersion was fed from a dropping funnel in the form of fine droplets into warm edible mineral oil which was continuously agitated. After all of the aqueous dispersion had been added to the oil, the oil was chilled to gel the vitamin-bearing beadlets. These were removed from the oil, washed by a method similar to that used in the above examples. Thereafter, the beadlets were suspended in 100 ml. of hexane contining 5 g. of dihydroxyacetone, previously dissolved in 15 ml. of a 50% ethanol-water mixture, and stirred for approximately 5 minutes. After the beadlets were separated and air dried, the beadlets were heated at 95° C. for 2 hours. The resulting beadlets were resistant to aqueous and acidic degradation but dissolved in Intestinal fluid U. S. P.

EXAMPLE V

The same procedure as described in Example IV was employed, except that the 5 grams of dihydroxyacetone in 15 ml. of a 50% ethanol-water mixture were admixed with the aforementioned aqueous mixture rather than the hexane. The beadlets obtained were substantially the same as those reported in Example IV.

EXAMPLE VI

A composition was prepared containing 80 grams of gelatin, 32 grams of honey, 30 grams of vitamin A acetate, 32 grams of vitamin D_2, 1.6 grams of 6 - ethoxy - 2,2,4-trimethyl - 1,2 - dihydroquinoline, 0.8 grams of n-propylgallate and 60 ml. of water. The mixture was stirred and heated until a uniform dispersion of the vitamins in the aqueous medium was obtained. 300 ml. of edible mineral oil with a viscosity of about 180 Saybolt units were added to the vitamin dispersion. The mixture was agitated at about 65° C. until fine droplets of the aqueous vitamin dispersion were formed in the oil. The oil was chilled rapidly to gel the beadlets, and the product was removed by filtration. The beadlets were suspended in 200 ml. of pentane containing 3 grams of acetaldehyde. After stirring the resultant slurry for 10 minutes, the beadlets were removed by filtration. Subsequently, they were washed with cold isopropanol and dried as described previously. After a final wash with acetone, the beadlets were heated at 85° C. for 3 hours.

The product so obtained consisted of fine beadlets containing a mixture of vitamins A and D. These beadlets displayed excellent mechanical strength and were insoluble in water and U. S. P. Gastric fluid but soluble in U. S. P. intestinal fluid.

In a similar manner, beadlets containing vitamin A cinnamate and vitamin E acetate were produced.

EXAMPLE VII

Boiled, distilled water was cooled to 60° C. and 2690 grams were mixed at this temperature with 1750 grams of gelatin. To the mixture were added 1400 grams of corn syrup while stirring. 834 Grams of crystalline vitamin A acetate, 16 grams of 6 - ethoxy-2,2,4 - trimethyl - 1,2 - dihydroquinoline and 10 grams of n-propyl gallate were then slowly added to the resultant solution which was kept in a closed container under a blanket of nitrogen. The mixture so formed was maintained at 65° C., while being agitated with an Eppenbach-type homogenizer. This homogenizer consists of a turbine-type device in which the liquid is drawn from beneath the apparatus and is passed through a four-blade turbine operating with but a slight clearance in such a manner that there is a strong shearing action on any particles. The melted vitamin A acetate was thereby dispersed throughout the aqueous solution in very finely divided form. After stirring for a short time, the liquid dispersion was allowed to flow through a wide tube and into a cylindrical vessel, closed at the bottom at the base of whose sides there are cut a series of fine holes. This cylinder was rotated and immersed to about half of its height in 6 United States gallons of edible mineral oil which was maintained at 65° C. A device of this type is described in U.S. Patent 2,299,929.

The edible oil used had a viscosity of 180 to 190 Saybolt units. The vessel holding the oil was covered with a tight fitting top and a blanket of nitrogen was maintained within this apparatus. The rotating cylinder into which the mixture was fed served to distribute the aqueous dispersion of vitamin A acetate in the form of fine droplets in the

edible mineral oil. The rotating cylinder also served to agitate the mineral oil and maintain the droplets in suspension. The fine holes through which the aqueous gelating dispersion was introduced into the oil were 0.006 inch in diameter, and the cylinder itself was 5 inches in diameter. A total time of 13.5 minutes was required to introduce the aqueous dispersion into the warm oil. Immediately after this addition had been completed, 150 ml. of a 37% formaldehyde solution were added. Then the oil was subjected to rapid cooling, so that its temperature dropped to 10° C. over a period of 25 minutes. During the cooling, an extra agitator which consisted of a suitable size propeller was used to stir the oil, thus maintaining the suspension until the droplets gelled. After the mixture had reached 10° C., 20 United States gallons of isopropanol, precooled to 10° C. were added. Agitation was maintained for 4 minutes more, and the product was then rapidly filtered on a porcelain filter.

The beadlets were washed with 4 litres of isopropanol at 10° C. This was repeated with the same volume of solvent. The product was then dried in a low humidity atmosphere at room temperature for 16 hours. The dried beadlets were give a final wash in a porcelain filter with one United States gallon of acetone. The product assayed about 550,000 units of vitamin A per gram and, when a sample was passed through a series of standard mesh screens, it was found that about 80% of the product was maintained on screens between 20 and 100 mesh in size (U.S. Standard). These beadlets exhibited no to disintegrate when added to intestinal fluid U. S. P., however, they immediately began to disintegrate wren added to intestinal fluid U. S. P.

The edible mineral oil used as a suspending medium for the formation of the beadlets may be recovered by distilling out the isopropanol and drying before reuse. The isopropanol is simultaneously recovered and must also be dried before reuse.

WHAT WE CLAIM IS: —

1. A process for preparing a vitamin preparation, which process comprises forming a particle comprising a vitamin as herein before defined, gelatin or other gellable, denaturable polypeptide colloid and an edible plasticizer for the said gelatin or other gellable, denaturable polypeptide colloid, the ratio of the weight of the said vitamin to the total weight of the materials constituting the particle being from 0.1 to 1 to 0.55 to 1, and rendering at least the surface layers of the particle insoluble in water and gastric fluid U.S.P. but soluble in intestinal fluid U.S.P. by contacting the exterior or the interior of the particle with a denaturing agent for the said colloid and, if necessary, heating the particle, or alternatively, rendering at least the surface layer of the particle insoluble in water and gastric fluid U.S.P. but soluble in intestinal fluid U.S.P. by heat treatment only.

2. A process according to claim 1, wherein the polypeptide colloid is gelatin, and glyoxal and/or formaldehyde are/is employed in an amount of 1% to 10% of the gelatin particle dry weight.

3. A process according to claim 1, wherein the polypeptide colloid is gelatin, dihydroxy acetone is employed in an amount of 1% to 30% of the gelatin particle dry weight and the gelatin particle is heated to a temperature from 75° to 105°C. for a period of a ½ to 4 hours.

4. A process according to claim 1, wherein the polypeptide colloid is gelatin, acetaldehyde is employed in an amount of 1% to 10% of the gelatin particle dry weight and the gelatin particle is heated to a temperature from 75°C. to 105°C. for a period of ½ to 4 hours to render it insoluble in water and gastric fluid U.S.P. but soluble in intestinal fluid U.S.P.

5. A process for the preparation of a vitamin preparation according to claim 1 substantially as described herein with particular reference to the Examples.

6. A vitamin preparation whenever prepared by a process according to any of the preceding claims.

7. A product according to claim 6, wherein the vitamin is an ester of vitamin A.

8. A product according to claim 7, wherein the said ester is vitamin A acetate or vitamin A palmitate.

9. A product according to any of claims 6—8 containing a pharmacologically acceptable antioxidant for the vitamin as herein-before defined.

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Abingdon: Printed for Her Majesty's Stationery Office, by Burgess & Son (Abingdon), Ltd.—1965.
Published at The Patent Office, 25 Southampton Buildings, London, W.C.2,
from which copies may be obtained.